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U1S S1328 S1330

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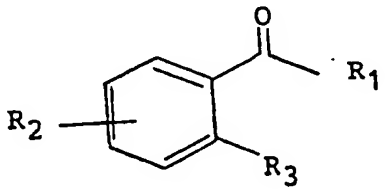
(58) Field of search
Online databases: CAS ONLINE

(54) Substituted benzene compounds as transferase inhibitors

(57) Substituted benzene compounds of the general formula:



(I)

wherein, subject to certain exceptions:
R_1 is amino, substituted amino, hydroxy or alkoxy;
R_3 is either hydrogen or together with R_1 is a group of the formula –Y–X–NH–, in which Y is CO, COH, NH, O or S, while X is CH_2, NH, N, CO, O or S, thus forming a ring; and
R_2 has various values including acylamino; alkanolamino; haloalkylamino; a mercapto amino derivative; substituted hydroxy; mercapto or substituted mercapto; guanidino or substituted guanidino; or ureido or substituted ureido.

These substituted benzene compounds act as inhibitors of nuclear ADP–ribosyl transferases and similar transferases, while they also show promise in the treatment of patients infected with a human immuno-deficiency virus (HIV).

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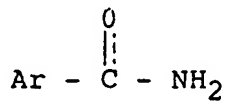
SUBSTITUTED BENZENE COMPOUNDS

The present invention relates to substituted benzene compounds and, in particular, to substituted benzamides, typically for use in inhibiting ADP - ribosyl transferases such as those known as poly(ADP-ribose) polymerase or synthetase.

The nuclei of all truly nucleated cells contain an enzyme which is generally known as poly(ADP-ribose)polymerase. The complete physiological function of this enzyme is not yet known, but published information indicates that it participates in DNA repair, DNA transfection, and perhaps in many other reactions involving DNA.

A number of inhibitors of this enzyme have been described. Most inhibitors so far described have the general formula of an aromatic amide, namely:



wherein Ar represents a monocyclic aromatic group, the amido group shown is bonded to a ring carbon atom of the aromatic group and Ar is either unsubstituted (except by the amido group) or is substituted by at least one simple substituent atom or group compatible with the inhibitory activity.

The group Ar may also be heterocyclic (with one or

two nitrogens in the ring) or dicyclic, with one heterocyclic ring containing up to two nitrogen atoms or a nitrogen and oxygen atom.

Examples of some important known inhibitors of poly(ADP-ribose)polymerase are:

Benzamide,

3-aminobenzamide,

3-bromobenzamide,

3-chlorobenzamide,

3-fluorobenzamide,

3-methylbenzamide,

3-methoxybenzamide,

3-hydroxybenzamide,

3-N-acetyl-aminobenzamide
(3-acetamido benzamide)

3-N-propionyl aminobenzamide
(3-propionamide benzamide)

Nicotinamide

5-methylnicotinamide

phthalhydrazide,

3-aminophthalhydrazide(luminol or 5-amino-2,3-dihydro-1,4- phthalazinedione),

3-nitrophthalhydrazide,

Chlorthenoxazine,

Benzoylenurea,
(2,4-[iH,3H] quinazolinedione)

Thymidine, and

Picolinamide.

The action of such inhibitors is known to be

reversible, competitive and to prevent the depletion of intracellular NAD that is caused by DNA-damaging agents. Using such inhibitors, poly(ADP-Ribose)polymerase has been shown to be involved in DNA excision repair (Shall, S. (1984) Adv. Rad. Biol. 11, pages 1 to 69) and in the antigenic switching of Trypanosoma brucei (Cornelissen, A.W.C.A. et al. (1985) Biochem. Pharm. 34, pages 4151 to 4156). Inhibition of nuclear poly(ADP-Ribose)polymerase by 3-aminobenzamide has also been shown to generate a large increase in spontaneous sister chromatid exchanges (Oikawa, A. et al (1980), Biochem. Biophys. Res. Commun. 97, pages 1131 to 1136, and Lindahl-Kiessling, K. & Shall, S. (1987) Carcinogenesis 8, pages 1185 to 1188). The latter two above-mentioned processes involve homologous DNA recombination.

In addition, it has recently been shown that the inhibition of poly(ADP-Ribose)polymerase by 3-methoxybenzamide or 3-aminobenzamide blocked the integration of foreign DNA into the genome during a calcium phosphate mediated DNA transfection procedure involving non-homologous/illegitimate DNA recombination (Farzeneh, F. et al (1988) Nucleic Acids Research 16, pages 11319 to 11326). This inhibition was shown to be specific to the integration step of DNA transfection. The uptake and expression of foreign DNA (introduced via plasmids) was not affected.

Some poly(ADP-Ribose)polymerase inhibitors have

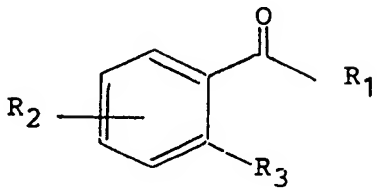
found a role in cancer therapy. DNA damage such as strand breaks, base damage and cross-linking due to X-ray or bleomycin exposure during radio- or chemotherapy is reparable. The poly(ADP-Ribose)polymerase inhibitors 3-aminobenzamide and nicotinamide have been shown to inhibit recovery of the damaged cells, and 3-aminobenzamide seems to work by delaying the rejoining of broken DNA strands.

In addition to poly(ADP-Ribose)polymerase, there are also other similar mono(ADP-Ribose)transferases which add mono ADP-Ribosyl groups onto specific aminoacid residues in various important cellular proteins. Furthermore, a number of important bacterial toxins are enzymes of this type.

We have now found that certain other novel benzamides act as inhibitors of nuclear ADP - ribosyl and similar transferases and, thus, are useful in medicine, for example, in the treatment of retroviral diseases and African trypanosomiasis, as an adjuvant in cancer therapy or in certain cases of immune disease, or in the treatment of conditions caused by certain bacterial toxins. In addition, in view of their inhibitory activity it is thought possible that one or more of the said compounds may be useful in the treatment of patients infected with a human immunodeficiency virus (HIV). Furthermore, certain non-inhibitory chemical analogues of said novel benzamides are useful as intermediates and as controls in toxicity

and other testing.

Accordingly, the present invention provides a compound of the general formula:



(I)

wherein:

R_1 is amino, substituted amino, hydroxy or alkoxy;

R_3 is hydrogen or together with R_1 is a group of the formula -Y-X-NH-, wherein Y is CO, COH, NH, O or S and X is CH_2, NH, N, CO, O or S, thus forming a ring; and

R_2 is acylamino including unsaturated acylamino (alkenoylamino) and haloacylamino; alkanolamino; haloalkylamino; a mercapto amino derivative, including thioalkylamino; substituted hydroxy, including alkylhydroxy, alkanolhydroxy, alkenylhydroxy, alkenoylhydroxy or a mercapto hydroxy derivative, including thioalkylhydroxy; mercapto and substituted mercapto, including alkanolmercapto, acylmercapto (including unsaturated acylmercapto, typically alkenoylmercapto) and haloalkylmercapto; guanidino or substituted guanidino; or ureido or substituted ureido, provided that when R_1 is amino and R_3 is hydrogen R_2 is not acetylamino,

R_2 also being hydroxy when R_1 and R_3 are together a group of the formula -Y-X-NH-.

In the compounds of the invention R_2 is preferably a substituted amino group of the formula R_4CZNH- in which:

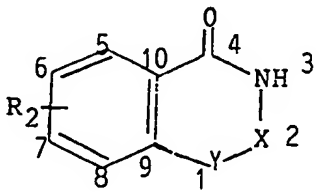
Z is oxygen, sulphur or NH;

R_4 is hydrogen, haloalkyl, alkenyl, amino or substituted amino (thus giving, for example, ureido and substituted ureido, as well as guanidino or substituted guanidino, depending on the value of Z); and
R_4 is also alkyl when R_1 and R_3 are together a group of the formula -Y-X-NH-

In the above preferred compounds of the invention Z is preferably oxygen. Also, R_1 and R_3 are together preferably a group of the formula $-\overset{\overset{O}{\|}}{C}-NH-NH-$.

R_1 when it is substituted amino preferably may be mono- substituted and the substituent is preferably an alkyl group, more preferably an alkyl group having from about 1 to about 6 carbon atoms. Similarly, when R_1 is alkoxy the alkoxy group preferably contains from about 1 to about 6 carbon atoms and, more preferably, is ethoxy.

Most preferably, R_1 is amino, hydroxy or ethoxy or together with R_3 is a group of the formula -X-Y-NH-, thus giving a compound of the formula:



(II)

As to group R_4, that is preferably hydrogen, chloromethyl, bromomethyl, 3-chloropropyl, 3-bromopropyl, 2-chloropropyl, propenoyl (acryloyl), butenoyl (crotonyl), amino, methylamino or N-methyl, N-nitroso amino. That is to say, in other words, R_2 is preferably

formylamino,

chloroacetylamino,

bromoacetylamino,

3-chloropropylamino,

3-bromopropylamino,

2-chloropropylamino,

3-propenoylamino,

3-butenoylamino,

3-ureido,

3-methylureido, or

3-N-methyl-N-nitroso-ureido.

Also, when R_1 and R_3 together form a ring, then R_2 is preferably:

hydroxy,

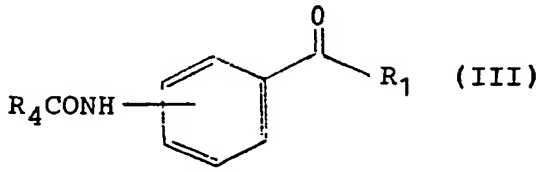
formylamino, or

acetylamino.

In the compounds of the invention as defined above the R_2 substituent is preferably in the meta position to the group $-CO-R_1$ when R_1 is not joined together with R_3. However, when R_1 and R_3 form a ring the preferred position of the substituent is position 5 or 8 in the

lefthand ring.

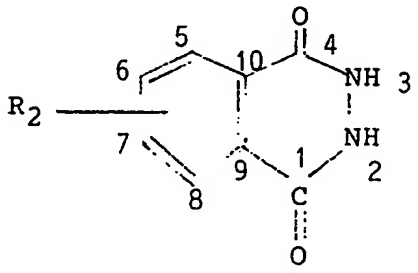
In more preferred aspects of the invention the compounds of formula I above may be **either** a compound of the formula:



(III)

wherein R_1 and R_4 are as defined above **or** a compound of the formula:

(IV)



wherein R_2 is formylamino or acetylamino or hydroxy.

In compounds of formula III the R_4-CONH substituent is preferably in the meta position. As to compounds of formula IV, there the R_2 substituent is preferably in the 5- or 8- position.

The following new compounds have been synthesised and are especially preferred in accordance with the invention:

1) 3-formylaminobenzamide;

2) 2-formylaminobenzamide;

3) 4-formylaminobenzamide;

4) 3-propenoylaminobenzamide;

5) 2-propenoylaminobenzamide;

6) 4-propenoylaminobenzamide;

7) 3-N(3-chloropropyl)aminobenzamide;

8) 3-ureidobenzamide;

9) 3-methylureidobenzamide;

10) 4-methylureidobenzamide;

11) Ethyl-m-propenoylaminobenzoate;

12) 3-propenoylaminobenzoic acid;

13) 3-butenoylaminobenzamide;

14) 3-chloroacetylaminobenzamide;

15) 3-bromoacetylaminobenzamide;

16) 3-N(3'-bromopropyl)aminobenzamide;

17) 3-N(3'-chloropropyl)aminobenzoic acid;

18) Ethyl, 3-methylureidobenzoate;

19) 3(N-methyl,N-nitroso ureido)benzamide;

20) 4(N-methyl,N-nitroso ureido)benzamide;

21) Ethyl,3-(N-methyl,N-nitroso ureido)benzoate;

22) 3-formylamino-phthalhydrazide [N-formyl-luminol or 5-formylamino-2,3-dihydro- 1,4-phthalazinedione];

23) 4-formylamino-phthalhydrazide [N-formyl-isoluminol or 6-formylamino-2,3-dihydro- 1,4-phthalazinedione];

24) 3-acetylamino-phthalhydrazide [or 5-acetylamino-2,3- dihydro- 1,4- phthalazinedione];

25) Ethyl-3-guanidinobenzoate;

26) 3-(guanidino)benzamide;

27) 1,5-dihydroxy-3-hydro-4-phthalazinone; and

28) 3(2-chloropropyl)aminobenzamide.

The compounds of the invention may be prepared by the following synthetic routes:

1. Compounds 1, 2, 3, 22 and 23 may be synthesised by formylation of the appropriate amide, with a mixture of formic acid and acetic anhydride (about 1:1) or by refluxing in formic acid.

2. Compounds 4, 5, 6, 7, 11, 12, 13, 16 and 17 may be synthesised by acylation of the appropriate amine and/or by the use of an appropriate acyl chloride derivative in acetone.

3. Compounds 14, 15 and 24 may be synthesised from the appropriate amine with acetic anhydride or with an appropriate acyl chloride derivative.

4. Compound 8 may be synthesised from 3-aminobenzamide and sodium cyanate in 33% acetic acid at 35°C.

5. Compounds 9, 10 and 18 may be synthesised by reacting the appropriate amine with methyl isocyanate.

6. Compounds 19, 20 and 21 may be synthesised by nitrosylation of the appropriate methyl ureido compounds, using sodium nitrite: the reactions occur in the solvents formic acid or dimethyl sulphoxide and sulphuric acid or in acetic anhydride.

7. Compounds 25 and 26 may be synthesised by refluxing 3-aminobenzamide hydrochloride with cyanamide in water. These compounds may also be made by refluxing

3-aminobenzamide and 2-methyl-2-thiopseudourea sulphate together in 30% ethanol.

8. Compound 27 may be synthesised by refluxing 3-hydroxyphthalic anhydride with hydrazine monohydrate in ethanol.

As indicated above the compounds of the invention are useful as inhibitors of ADP - ribosyl transferases. As such they are believed to be useful in the treatments set out above at levels ranging from 0.01 to 5 mmoles per kg. For example, at a level of about 0.02 mmoles per kg for compound 27 above.

Accordingly, the invention includes a pharmaceutical composition, which composition comprises a compound according to the invention and a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be formulated with solid or liquid diluents or carriers as is well known in the art. Furthermore, the formulated compositions may be put up in unit dosage forms such as tablets, capsules etc. as is also well known.

Some of the compounds of the invention act as reversible inhibitors in the same manner as known compounds. Surprisingly, however, certain of the compounds, namely those of formula (IV) below, in particular compounds 4 to 7, 11 to 17 and 19 to 21 are able to form covalent compounds. Moreover, compounds 4, 7, 14, 15, 16 and 19 exhibit a preferred feature in that they act by forming a covalent compound with the enzyme

specifically and thus inhibit the enzyme. These are new and unexpected features.

In view of the above new and unexpected features, especially preferred compounds in accordance with the invention are those of the general formula III set out above, wherein R_1 is amino, hydroxy or alkoxy and R_4 is haloalkyl, alkenyl, or substituted amino.

More preferred compounds of the above formula are as follows:

3-propenoylaminobenzamide;

2-propenoylaminobenzamide;

4N(3-chloropropyl)aminobenzamide;

3-N(3-chloropropyl)aminobenzamide

Ethyl-m-propenoylaminobenzoate;

3-propenoylaminobenzoic acid;

3-butenoylaminobenzamide;

3-chloroacetylaminobenzamide;

3-bromoacetylaminobenzamide;

3-N(3'-bromopropyl)aminobenzamide;

3-N(3'-chloropropyl)aminobenzoic acid;

3-(N-methyl,N-nitroso ureido)benzamide;

4-(N-methyl,N-nitroso ureido)benzamide; and

Ethyl,3-(N-methyl,N-nitroso ureido)benzoate.

In the compounds of the invention the utility exhibited may be in terms of one or more of:

Inhibitory activity,

Utility as an intermediate, and/or

Utility as a control compound.

Generally speaking, the meta or 5- or 8- compounds defined or described above will exhibit inhibitory activity, whereas the ortho or para compounds (6- or 7-substituted compounds in the two ring compounds) may find better use as intermediates or controls. However, it may be the case that some of the ortho compounds also will exhibit useful inhibitory activity. Also, those compounds wherein R_1 is amino are good inhibitors, whereas those compounds wherein R_1 is other than amino are better used as intermediates and controls.

Moreover, the compounds which exhibit inhibitory activity are not necessarily those which form covalent compounds and vice versa. Thus, for example, compounds 12, 17, 20 and 21 form covalent compounds, but are not enzyme inhibitors.

The compounds and processes in accordance with the invention will now be illustrated by the following specific Examples.

Example 1

Synthesis of 3-formylaminobenzamide (Compound 1)

A mixture of 40ml of acetic anhydride and 40 ml of 98 to 100% formic acid was heated at 50 to 60°C for 90 minutes. The solution was cooled to room temperature and 10 gm of 3-aminobenzamide was added in small aliquots over 15 minutes. The temperature was kept below 30°C by occasional cooling in an ice-bath during the addition of the 3-aminobenzamide. The solution was

stirred at room temperature for 2.5 hours, and then it was evaporated under vacuum to a viscous oil. Traces of acetic anhydride and of formic acid were removed by the repeated addition of water and evaporation until a white solid product was obtained. The solid product was crystallized from water. The white, round crystals were filtered off and washed with cold water and then dried under a vacuum. The overall yield was 78% and the melting point of the final material was 175°C to 177°C. Mass spectrum analysis indicated a molecular weight of 164.

Example 2

Synthesis of 3-formylaminobenzamide (Compound 1)

10 gm of 3-aminobenzamide and 80 ml of 98 to 100% formic acid were refluxed for 60 minutes. The formic acid was removed by evaporation under vacuum; the residual oily product was mixed with water and evaporated to yield a solid residue. This solid was crystallized from water to give 8.2 gm (yield=68%) of white, round crystals with a melting point of 176°C to 177°C. Mass spectrum analysis indicated a molecular weight of 164.

Example 3

Synthesis of 2- and 4-formylaminobenzamide (Compounds 2 and 3)

2- and 4(N-formylamino)benzamide were prepared by

the method described in Example 2, except that the starting material was respectively 2- and 4-aminobenzamide.

Example 4

Synthesis of 3-propenoylaminobenzamide (Compound 4)

Propenoyl chloride from Aldrich Chemical Company Ltd. (2.2 gm, 24.3 mMole) was added dropwise to an ice-cold solution of 3-aminobenzamide (5.0 gm, 36.8 mMole) in 30 ml of acetone. The mixture was stirred on ice for 30 minutes, and then the white precipitate was filtered off and washed with cold acetone and then with cold water to give 4.2 gm of white product. The product was crystallized from 25% aqueous dimethyl sulphoxide and the crystallized product had a melting point of 229°C to 230°C. The overall yield was 44%.

Example 5

Synthesis of 3-propenoylaminobenzoic acid (Compound 12)

This was synthesized by a procedure similar to that used in Example 4 to give a product having a melting point of 247°C to 248°C.

Example 6

Synthesis of 2- and 4-propenoylaminobenzamides (Compounds 5 and 6).

These compounds were synthesised in the same way as that used to make 3(N-propenoylamino)benzamide in Example 4, starting from 2- and 4-aminobenzamide. The observed melting points were: 2- compound 172° to 173°C

and 4- compound 254°C to 255°C.

Example 7

Synthesis of 3-butenoylaminobenzamide (Compound 13).

This was achieved by the same procedure as that used to make 3-propenoylaminobenzamide, namely the route of Example 4, except that 2.30 gm (20 mMole) of butenoyl chloride was used. The product obtained had a melting point of 211°C to 212°C.

Example 8

Synthesis of Ethyl 3-propenoylaminobenzoate (Compound 11).

Propenoyl chloride (668 mg, 600 ul, 7.4 mMole) was added dropwise to an ice-cold solution of ethyl 3-aminobenzoate (2.0 gm, 12 mMole) in 10 ml of acetone. The solution was stirred for 30 minutes on ice and then for 30 minutes at room temperature. 50 ml of water was added and the yellowish oil was separated by decantation. It was washed with water and then dissolved in 15 ml of diethl ether. This solution was washed with 10% (w/v) sodium bicarbonate, water and then dried over anhydrous sodium carbonate. The ether was evaporated and a white creamy product was crystallized from ethanol. The overall yield was 37%, and the melting point of the product was 93°C to 94°C.

Example 9

Synthesis of 3-N(3-chloropropyl)aminobenzamide (Compound 7).

3-chloropropyl chloride (Lancaster Synthesis) (800 ul, 8.4 mMole) was added dropwise to an ice-cold solution of 3-aminobenzamide (1.5 gm, 11 mMole) in 15 ml of acetone. After stirring for 30 minutes on ice, the white precipitate was filtered off and washed with cold acetone and with water. Crystallization from 10% (v/v) ethanol yielded 1.1 gm of fine white needles; overall yield was 44%. The final product had a melting point of 188°C to 189°C.

Example 10

Synthesis of 3-N(3'-bromopropyl)aminobenzamide (Compound 16).

The same procedure as in Example 9 above was used except that 3-bromopropyl chloride was the reactant. The melting point of the product was 188°C to 189°C.

Example 11

Synthesis of 3(2-chloropropyl)aminobenzamide (Compound 28).

The same procedure as in Example 9 above was used except that 2-chloropropyl was the reactant. The final product had a melting point of 193°C to 194°C.

Example 12

Synthesis of 3-ureidobenzamide (Compound 8).

Sodium cyanate (1.3 gm, 20 mMole) in 9.0 ml of water was added over a 15 minute period to a solution of

3-aminobenzamide (1.36 gm, 10 mMole) in 33% acetic acid at 35°C. The mixture was stirred for a further 15 minutes during which time a white precipitate formed. This was filtered off, washed with cold water and crystallized from 25% ethanol to give 1.4gm (78%) of shiny crystals. m.p. $> 300^{\circ}C$.

Example 13

Synthesis of 3-methylureidobenzamide (Compound 9).

Methyl isocyanate (2.0 ml, 33.8 mMole) was added to a stirred solution of 3-aminobenzamide (4.5 gm, 33.0 mMole) in 40 ml of acetone. A white precipitate was formed in a few minutes; the reaction was continued with stirring for a further 30 minutes. The white precipitate was filtered off, washed with cold water and crystallized from 40% ethanol. Yield was 4.0 gm (62.5%); m.p. 230°C to 231°C.

Example 14

Synthesis of 3-formylamino-phthalhydrazide (Compound 22).

Process 1.

1.0 gm of 3-aminophthalhydrazide and 70.0 ml of 98% formic acid was refluxed for 60 minutes. The solution was cooled to room temperature and then to ice temperature. The precipitate was filtered off at 4°C, and washed with cold water. It was then dried under vacuum, giving 1.15 gm (99.0%) of a bright yellow product which was crystallized from dimethylsulphoxide.

Melting point 293°C to 294°C.

Process 2.

A mixture of 60 ml acetic anydyride and 60 ml of 98% formic acid was heated at 50°C to 60°C for 90 minutes. 1.0 gm of 3-amino phthalhydrazide was added to the warm solution (50°C) with stirring. The reaction was then stirred at 37°C for 3 hours. A yellow precipitate came out, which was cooled to 4°C and filtered off. The product was washed with cold water and crystallized from dimethylsulphoxide. Process 1 gave a higher yield.

Example 15

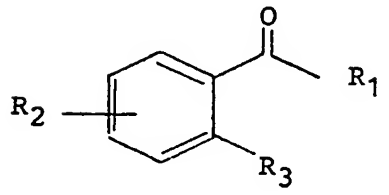
Synthesis of 1,5-dihydroxy-3-hydro-4-phthalazione (Compound 27)

3-hydroxyphthalic anhydride (1.0 gm, 6.1 mmole) was dissolved in 25 ml ethanol by heating and stirring. Hydrazine hydrate (0.315 ml, 6.5 mmole) in 5 ml of ethanol was added dropwise to the clear solution. The mixture was refluxed in a water bath for 60 minutes, and was then cooled to 4°C. The precipitate was filtered off, washed with cold water, then with cold ethanol and dried under vacuum, giving 0.99 gm (90%) of white product, with a m.p. of 321 to 321°C. Crystallization from a water-ethanol mixture produced fine, white needle crystals with a m.p. of 329 to 331°C.

As will be appreciated, the invention is not limited to the specific details set out above by way of illustration only and numerous variations may be made within the spirit and scope of the claims which follow.

CLAIMS

1. A compound of the general formula:



(I)

wherein:

R_1 is amino, substituted amino, hydroxy or alkoxy;

R_3 is hydrogen or together with R_1 is a group of the formula -Y-X-NH-, wherein Y is CO, COH, NH, O or S and X is CH_2, NH, N, CO, O or S, thus forming a ring; and

R_2 is acylamino including alkenoylamino and haloacylamino; alkanolamino; haloalkylamino; a mercapto amino derivative, including thioalkylamino; substituted hydroxy, including alkylhydroxy, alkanolhydroxy, alkenylhydroxy, alkenoylhydroxy or a mercapto hydroxy derivative, including thioalkylhydroxy; mercapto and substituted mercapto, including alkanolmercapto, acylmercapto, (including alkenoylmercapto) and haloalkylmercapto; guanidino or substituted guanidino; or ureido or substituted ureido, provided that when R_1 is amino and R_3 is hydrogen R_2 is not acetylamino,

R_2 also being hydroxy when R_1 and R_3 are together a group of the formula -Y-X-NH-.

2. A compound according to claim 1, wherein R_2 is a

substituted amino group of the formula R_4CZNH- in which:

Z is oxygen, sulphur or NH;

R_4 is hydrogen, haloalkyl, alkenyl, amino or substituted amino; and

R_4 is also alkyl when R_1 and R_3 are together a group of the formula -Y-X-NH-

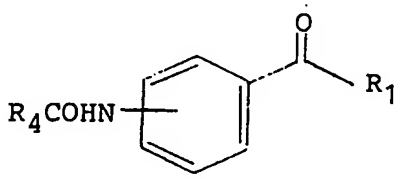
3. A compound according to claim 2, wherein Z is oxygen.

4. A compound according to any one of the preceding claims, wherein R_1 and R_3 are together a group of the formula $-\overset{\overset{O}{\|}}{C}-NH-NH-$.

5. A compound according to any one of the preceding claims, wherein R_1 is amino, hydroxy or ethoxy or together with R_3 is a group of the formula -X-Y-NH- .

6. A compound according to any one of claims 2 to 5, wherein R_4 is hydrogen, chloromethyl, bromomethyl, 3-chloropropyl, 3-bromopropyl, 2-chloropropyl, propenoyl (acrylolyl), butenoyl (crotonyl), amino, methylamino or N-methyl, N-nitroso amino.

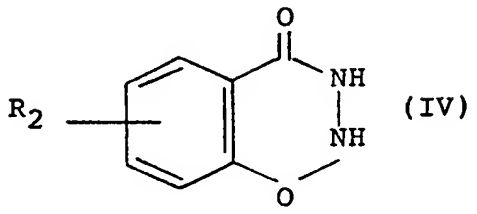
7. A compound according to claim 1 of the formula:



(III)

wherein R_1 and R_4 are as defined in any of the preceeding claims.

8. A compound according to claim 1 of the formula:



(IV)

wherein R_2 is formylamino, acetylamino or hydroxy.

9. A compound according to any one of claims 1 to 7 of the general formula III defined in claim 7, wherein R_1 is amino, hydroxy or alkoxy and R_4 is haloalkyl, alkenyl, or substituted amino.

10. A compound according to any one of the preceding claims, wherein the R_2 substituent is in the meta position to the group $-CO-R_1$ when there is no righthand ring and in the 5- or 8- position when there is a righthand ring.

11. A compound according to claim 1, which is:

3-formylaminobenzamide;

2-formylaminobenzamide;

4-formylaminobenzamide;

3-propenoylaminobenzamide;

2-propenoylaminobenzamide;

4-propenoylaminobenzamide;

3-N(3-chloropropyl)aminobenzamide;

3-ureidobenzamide;

3-methylureidobenzamide;

4-methylureidobenzamide;

Ethyl-m-propenoylaminobenzoate;

3-propenoylaminobenzoic acid;

3-butenoylaminobenzamide;

3-chloroacetylaminobenzamide;

3-bromoacetylaminobenzamide;

3-N(3'-bromopropyl)aminobenzamide;

3-N(3'-chloropropyl)aminobenzoic acid;

Ethyl, 3-methylureidobenzoate;

3(N-methyl,N-nitroso ureido)benzamide;

4(N-methyl,N-nitroso ureido)benzamide;

Ethyl,3-(N-methyl,N-nitroso ureido)benzoate;

3-formylamino-phthalhydrazide [N-formyl-luminol];

4-formylamino-phthalhydrazide;

[N-formyl-isoluminol]

3-acetylamino-phthalhydrazide;

3-guanidinobenzoate;

3-(guanidino)benzamide; or

1,5-dihydroxy-3-hydro-4-phthalazinone.

12. A compound according to claim 1, which is:

3-propenoylaminobenzamide;

2-propenoylaminobenzamide;

4N(3-chloropropyl)aminobenzamide;

3-N(3-chloropropyl)aminobenzamide

Ethyl-m-propenoylaminobenzoate;

3-propenoylaminobenzoic acid;

3-butenoylamino)enzamide;

3-chloroacetylaminobenzamide;

3-bromoacetylaminobenzamide;

3-N(3'-bromopropyl)aminobenzamide;

3-N(3'-chloropropyl)aminobenzoic acid;

3-(N-methyl,N-nitroso ureido)benzamide;

4-(N-methyl,N-nitroso ureido)benzamide;

Ethyl,3-(N-methyl,N-nitroso ureido)benzoate; or

1,5-dihydroxy-3-hydro-4-phthalazinone.

13. A compound according to claim 1 and substantially as hereinbefore described.

14. A compound according to claim 1 and substantially as hereinbefore described with reference to the specific Examples.

15. A compound according to any one of the preceeding claims for use as an enzyme inhibitor.

16. A compound according to any one of claims 1 to 14 for use in the treatment of retroviral diseases or African trypanosomiasis, as an adjuvant in cancer chemotherapy or in certain cases of immune disease, or in the treatment of conditions caused by certain bacterial toxins.

17. A pharmaceutical composition, which composition comprises a compound according to any one of the preceding claims and a pharmaceutically acceptable diluent or carrier.

18. A compound according to any one of claims 1 to 14 for use as an intermediate.

19. A compound according to any one of claims 1 to 14 for use as a control compound.

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